What can we learn from past pandemics, relevant to Covid-19?

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Game plan

- Examine recent article on 1918 flu pandemic, and other epidemics, as related to Covid-19
- We will consider a variety of pathogens that have taken huge tolls on human life over the centuries, but focus most on 1918 influenza pandemic

Objectives

- Recite key findings from a recent article on past pandemics as related to Covid-19 pandemic
- Summarize similarities and differences between the 1918 flu pandemic and Covid-19
- List candidate pathogens for upcoming pandemics during the next 20 years
- Pass a quiz at the end

Take home messages

- The pace of emergence of new pandemics is likely to be on the increase due to multiple host, agent, and environmental changes
- We can expect a series of pandemic challenges in the next decades, based on recent human and pathogen histories
- When viruses and other pathogens 'jump species', the results for the new host species can be very harmful
- Herd immunity and improved sanitation likely ended the 1918-19 flu pandemic after the third global wave..tho the viral descendants of that pandemic are still with us
- Herd immunity, improved adherence to sanitation/prevention methods, and perhaps vaccine will result in slow down of Covid-19, and future pandemics

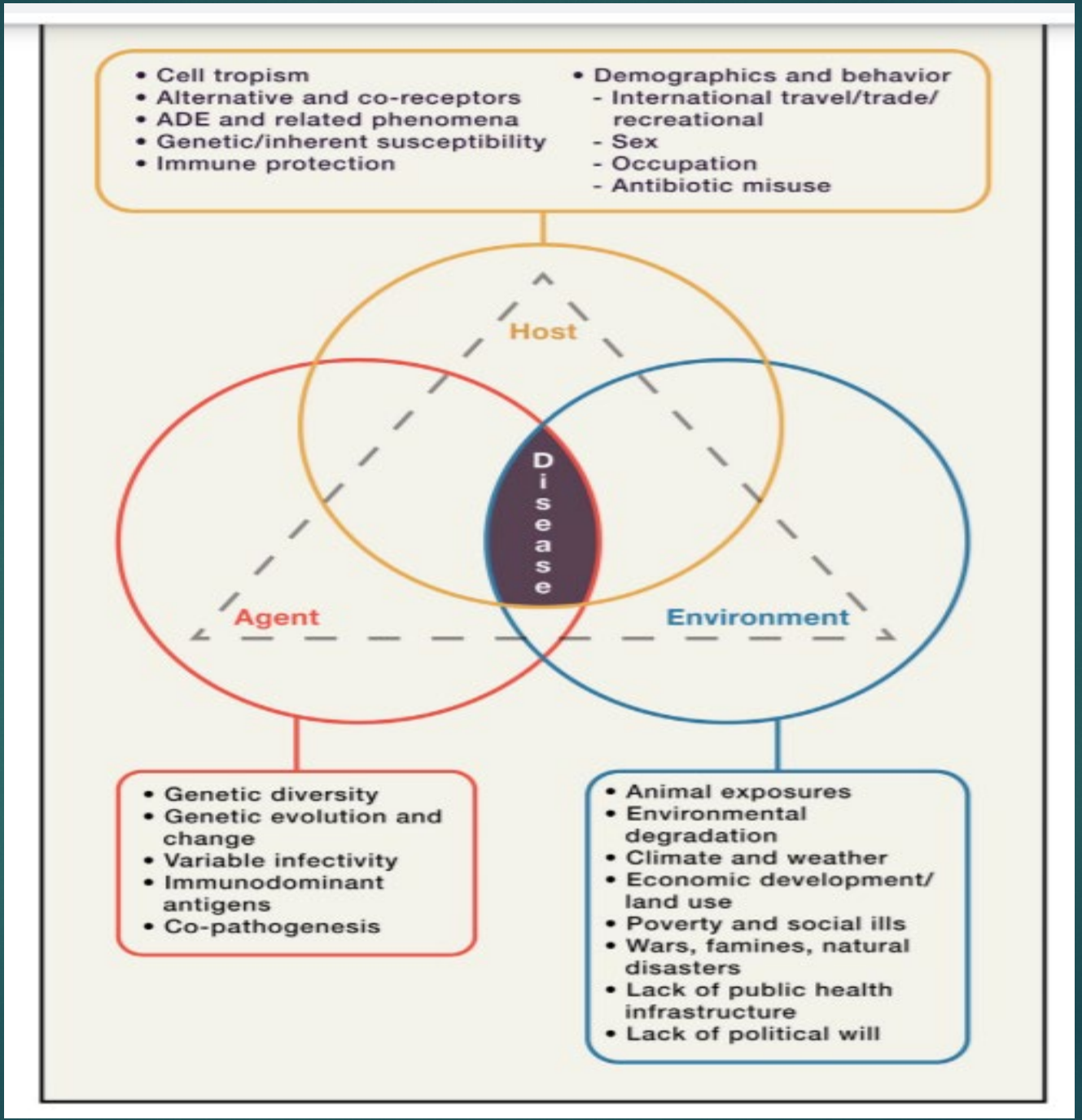
Introduction

- “Pandora’s box’ lid continues to open and let out new pathogens, as has been the case for millennia
- Although none of us has the crystal ball to predict the next pandemic cause and develop vaccine ahead of time, the SARS and MERS epidemics provided a bit of coronavirus-related warning
- Influenza virus remains a major pandemic threat (even now), with four pandemics worldwide since 1918
- Humans continue to create environmental and other changes that put us in the pathway of many epidemics to come

Table 1. Emerging Infectious Diseases in History

Year	Name	Deaths	Comments
430 BCE	"Plague of Athens"	~100,000	First identified trans-regional pandemic
541	Justinian plague (*Yersinia pestis*)	30–50 million	Pandemic; killed half of world population
1340s	"Black Death" (*Yersinia pestis*)	~50 million	Pandemic; killed at least a quarter of world population
1494	Syphilis (*Treponema pallidum*)	>50,000	Pandemic brought to Europe from the Americas
c. 1500	Tuberculosis	High millions	Ancient disease; became pandemic in Middle Ages
1520	*Hueyzahuatl* (*Variola major*)	3.5 million	Pandemic brought to New World by Europeans
1793–1798	"The American plague"	~25,000	Yellow fever terrorized colonial America
1832	2nd cholera pandemic (Paris)	18,402	Spread from India to Europe/Western Hemisphere
1918	"Spanish" influenza	~50 million	Led to additional pandemics in 1957, 1968, 2009
1976–2020	Ebola	15,258	First recognized in 1976; 29 regional epidemics to 2020
1981	Acute hemorrhagic conjunctivitis	rare deaths	First recognized in 1969; pandemic in 1981
1981	HIV/AIDS	~37 million	First recognized 1981; ongoing pandemic
2002	SARS	813	Near-pandemic
2009	H1N1 "swine flu"	284,000	5th influenza pandemic of century
2014	Chikungunya	uncommon	Pandemic, mosquito-borne
2015	Zika	~1,000?*	Pandemic, mosquito-borne

Selected important emerging and re-emerging infectious diseases of the past and present, 430 BCE–2020 CE. Mortality estimates are in most cases imprecise; see text.


• Cell tropism
• Alternative and co-receptors
• ADE and related phenomena
• Genetic/inherent susceptibility
• Immune protection
• Demographics and behavior
- International travel/trade/ recreational
- Sex
- Occupation
- Antibiotic misuse
Host
Disease
Agent
Environment
• Genetic diversity
• Genetic evolution and change
• Variable infectivity
• Immunodominant antigens
• Co-pathogenesis
• Animal exposures
• Environmental degradation
• Climate and weather
• Economic development/ land use
• Poverty and social ills
• Wars, famines, natural disasters
• Lack of public health infrastructure
• Lack of political will

Intro to influenza-some tidbits

- RNA, Orthomyxoviruses that are enveloped
- Types A (humans and animals), B (humans), C (humans)
- H and N protein spikes on surface that have attachment and replication-related functions
- 16 H antigens, 9 N antigens, resulting in many different potential combinations
- An invading influenza virus can result in production of a million viruses in a host cell, within 12 hours…thus, high potential for mutations
- The 1918 virus, H1N1, similar to an avian influenza with very high lethality

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- Antigenic drift refers to smaller mutations that occur yearly in influenza A, H and N antigens…like H1N1 to H1N2
- Antigenic shifts refer to major genetic changes that are more likely to give rise to pandemics, like H5N2, that are not recognized by our immune systems
- All pandemics since 1918 have remnants of the 1918 virus with RNA from swine
- Scientists have ferret model for studying antigenic shifts and the outcomes of engineered viruses (potentially very dangerous activity as some of these viruses have high mortality)

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- Flu is transmitted by respiratory droplets and personal contact (like from shaking hands then self inoculating)
- Fomite spread thru handling common objects and self-inoculating
- Aerosols of lesser importance
- Cold air and crowding favor influenza virus—thus, the wintertime spikes in occurrence
- With current global travel, viruses like influenza viruses can move around the planet very quickly

Influenza pandemic of 1918—fascinating!

- H1N1 first wave in spring, origin debated, somewhat mild course
- Second wave in the fall, 1918, much more severe
- Third wave winter and spring, 1919, from Australia, less severe
- Estimated 1/3 of world population infected
- 50-100 million deaths (projected to today, 220-440 million deaths), with a fatality:case of 5 to 10%
- Substantial proportion of deaths due to bacterial lung infection on top of flu, often occurring later in the course
- Decline of pandemic likely due to development of herd immunity and improved sanitary practices…in addition to end of war and international travel of soldiers and support personnel

Influenza pandemic, cntd

- Armistice day Nov 11, 1918…the world had been at 'total war'
- Troops did not go back home immediately and Wilson continued to pile troops onto ships bound for Europe during that fall of 1918 (he was aware of the risks to soldiers)
- In US, later victory celebrations with return of troops likely fed the continued infection rate, as well as parades in Europe involving millions of people
- Masks accomplished very little…they were made of gauze
- Warm weather degrades outer coating and the viruses' ability to float through the air, so disease spread was and is more efficient in the winter months

Factors that promoted 1918 pandemic, in the US

- President Wilson would not publicly recognize the severity of the disease and did nothing to intervene (despite his getting the infection and becoming gravely ill). He did not want to lesson his pro-war messages. Sedition Act prohibited telling the truth about the infection.
- War bond parades in major cities nationwide in fall 1918 brought large crowds together, singing and partying like it was 1969
- Most major newspapers downplayed the pandemic, saying it was just seasonal flu (likely related to the Sedition Act)
- Some public health measures put into place related to quarantines, covering coughs, masks, no spitting campaigns..but masks were gauze masks and no consistent messaging was in effect

Further adding to the chaos of pandemic

- The ‘total war’ resulted in mass hunger, huge typhus epidemics with high morbidity and mortality, destruction of many European cities, displaced populations, and general debility of much of the planet related to total war…still going on in 1918 and post-war.
- After the war but still during the pandemic, Paris Peace talks and Treaty of Versailles brought 10,000 people into the discussions from multiple countries. Photos showed no masks
- Welcome receptions for President Wilson in France included 2 million people standing shoulder to shoulder and cheering…photos showed no masks.

Waves of Spanish flu

- First wave: spring of 1918, not so virulent but some regional pockets of virulent infections in Philadelphia and Boston
- Second wave, early fall, 1918, highly virulent, very lethal with high fatality:case ratios. (Switzerland in trouble by July of that year)
- By September, 1918, pandemic full speed ahead in Boston, and in Sierra Leone, with rapid movement across the globe
- Third wave: spring of 1919, started in Australia, and may represent another mutation of the virus.

Major influenza pandemics

- 1918 Spanish flu, H1N1 (thru 1920 or later)
- 1957 Asian influenza, H2N2 (avian and human)
- 1968 Hong Kong flu, H3N2 (avian and human)
- 2009 Mexican flu H1N1 (swine, human, avian, and Euroasian swine, reassorted into new virus)

- Starting in 1580 in Europe, the planet has experienced 12 widespread influenza epidemics/pandemics

‘False start’ flu epidemic, 1976

- Swine flu, Ft. Dix, New Jersey origin of this H1N1 (very unusual event!)
- 40 million Americans immunized at public venues

  (Most of them seemed to be in line right ahead of me at the Albuquerque fairgrounds)
- The epidemic did not come, and the increase of G-B cases seems to have hampered vaccine uptake ever since

Clinical picture partly resembled Covid-19

- Cytokine storms
- Neurologic sequelae (including for President Wilson)
- Multi-organ system involvement
- Pulmonary involvement prominent, but unlike Covid, secondary bacterial infection common, consistently resulting in death

Differences in clinical picture between 1918 flu and Covid-19

- 1918 flu HIGHLY lethal, esp for 18-45 year old people, esp during second wave
- Rapid onset of advancing illness within hours of admission
- Severe cyanosis
- Bleeding from nostrils, ear canals, eye sockets
- Death within hours…many cases of disease running its course in 12 hours only
- Corpses piled up, medical personnel died at high rates

Treatment for Spanish flu

- Hydration
- Aspirin
- The end

- In 1918, there was no ICU, no vents, no antivirals, no vaccine, no oxygen administration, no antibiotics for treating bacterial pneumonias. There were not even many civilian doctors…they were sent to the war.

Behavioral and societal responses to Spanish flu

- Closing of schools, churches, theatres, sporting events, businesses. But determined on a city-by-city basis
- Promotion of mask wearing, with rebellions against mask wearing
- Eventual ban on public meetings, also met with rebellion (think Sturgis and Ozark motorcycle rider gatherings or certain recent political events)
- After businesses re-opened in some cities, new closure orders were issued and further rebellions to that were common

Decline of Spanish flu probably related to

- Herd immunity, particularly as a result of first wave of infection that was less virulent, but, immunogenic
- Mutation of virus after two years toward less virulence
- End of WWI and extensive travel

(Flu season of 1920-21 still bad, as with 1928)

Social, political, and other upheavals contributed to Spanish flu

- WWI climate, censorship, lack of leadership in disease/infection control
- Government leadership would not disclose the truth to the public
- No effective containment strategies
- No effective treatments
- Social rebellion against public health measures

Fertile soil for current and future pandemics related to:

- Lack of antiviral treatment
- Lack of vaccines
- Human intrusion into animal environments, directly or indirectly by destroying animal habitats
- Ability of pathogens to mutate quickly
- Ability of many pathogens to jump species (herpes, HIV, SARS, MERS, Ebola) or adapt to human hosts (plague, many zoonoses)
- The estimated existence of hundreds of thousands of different microbes that we have not identified yet
- Re-emergence of old pathogens that have not circulated for many years, with new pathogens with genetic mutations
- Climate change and population shifts to urban areas

Summary comments

- We are creating many opportunities for microbes to emerge into niches that we make…these new niches are 'in our faces' now.
- Social and environmental changes can be seen in VAST urbanization movement around the globe, climate change, animal habit destruction that forces adaptive behavioral responses of the affected animal species
- We are rapidly changing the planet, and unfortunately, must change it to survive as a species. We are extracting a huge toll, tho.
- Our human-dominated world and the changes we make in our environment can and do cause extreme backlashes

Quotable quotes

- “in the ancient ongoing struggle between microbes and humans, genetically more adaptable microbes have the upper hand in consistently surprising us and often catching us unprepared”

  David Morens, 2020

Time for a quiz. Write down whether the trait is associated with a) Spanish flu of 1918, b) Covid-19, c) neither, or d) both: (75% to pass, no arguing)

- Cytokine storms
- High infectivity (high R0)
- High fatality: case ratio
- Successful containment strategies
- Politicians downplayed severity
- Vaccine development efforts
- Herd immunity the key to end of pandemic
- Primarily a disease of young people

References

- Grand rounds, UCSF department of medicine, on influenza pandemic and Covid-19, interview with John Barry
- Prep talks, with John Barry, April 2020 (you tube)
- Great courses, Introduction to Infectious Diseases, Influenza.
- Morens and Fauci. Emerging pandemic diseases: How we got to Covid-19. Cell, 2020.08.021

- Grazie a Grazia Ori . “Non mangia I pipistrelli!”